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Case Report

Pheochromocytoma in the organ of Zuckerkandl with distant skeletal metastases – A case report ☆,☆☆

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ABSTRACT

Pheochromocytomas are rare catecholamine-secreting neuroendocrine tumors that originate from chromaffin cells in the adrenal medulla. They cause severe hypertension and various clinical manifestations. While most arise in the adrenal medulla, some occur in extra-adrenal locations.We present a case report with clinical, laboratory and radiographic data, along with a brief literature review. We report a 33-year-old woman who presented with flushing and sharp lower abdominal pain. Abdominal ultrasound and urinary metanephrines suggested a pheochromocytoma. Subsequent Computed tomography (CT) and Ga-DOTATATE Positron emission tomography/Computed tomography (PET/CT) scans confirmed a pheochromocytoma in the organ of Zuckerkandl with distant bony metastasis. Extra-adrenal pheochromocytomas, or paragangliomas, are rare tumors found in specific anatomical locations. Their diagnostic challenges stem from variable clinical presentations and imaging findings. CT scans and Ga-DOTATATE PET/CT scans are crucial in diagnosis and prognosis. Surgical resection can cure localized cases, while metastatic disease requires palliative options, such as chemotherapy and I131-MIBG, due to a poorer prognosis.

Introduction

Pheochromocytomas are exceptionally uncommon neuroendocrine tumors that secrete catecholamines. The majority of these tumors, approximately 85-90%, originate from the adrenal medulla and are referred to as intra-adrenal pheochromocytomas. In rare cases (around 10%), they can arise from locations outside the adrenal glands and are known as extra-adrenal pheochromocytomas or paragangliomas [1].

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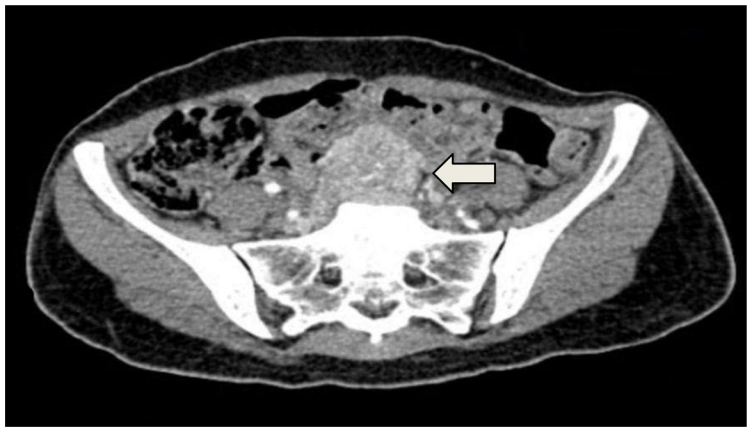

Fig.1 – CT scan of the abdomen and pelvis with contrast showed an irregular hypodense mass lesion inferior to the bifurcation of the aorta at the lumbosacral junction of the prevertebral area.

About half of these extra-adrenal paragangliomas occur in the organ of Zuckerkandl [2], which consists of parasympathetic paraganglia situated anterolaterally to the distal abdominal aorta between the origin of the inferior mesenteric artery or renal artery and the aortic bifurcation.

Due to the diverse clinical presentations, imaging features, and pathological appearances, accurately diagnosing these tumors can be challenging. Nevertheless, appropriate and timely diagnosis is crucial to prevent severe complications such as myocardial infarction, stroke, and fatality. In this report, we present a unique case of an extra-adrenal pheochromocytoma located in the organ of Zuckerkandl.

Case presentation

A 33-year-old female presented to the hospital with complaints of flushing and sharp lower abdominal pain below the umbilicus. The pain increased when she moved and during urination but was partially relieved with medication. The patient had a history of hypertension for four years and had previously sought medical attention for it. However, the oral medication she was provided with only partially relieved her symptoms. On physical examination, the patient was found to be tachycardic, and her blood pressure was high at 160/90. Her abdomen was soft and nontender, and no masses were felt during palpation. Systemic examination was otherwise normal. Routine investigations, including complete blood count, serum electrolytes, and liver and renal function tests, were within the normal range.

Further evaluation of the patient's abdominal pain was done through imaging. An ultrasound at a private lab revealed a normal-sized uterus in mid-position, with a 6 mm endometrial thickness. However, a large mixed echogenicity mass-like area was found separable from the anterior wall of the uterus, measuring approximately 6.2 × 5.6 cm in size. The differential diagnosis included a subserosal fibroid or an extra-adrenal Pheochromocytoma. Additionally, a complex cyst was found in the left adnexa measuring 5.7 × 5 cm, with fairly thick walls and internal septa.

Subsequent laboratory work revealed elevated urine normetanephrines of >4800 μg/24 hours (normal 110-1050 μg/24 hours). Urine metanephrines (319 μg/24 hours, normal 35-460 μg/24 hours) and urine dopamine (237.78 μg/24 hours, normal 65 to 400 μg/24 hours) were normal. Another ultrasound was conducted at our institution, revealing a solid echogenicity mass on the right side of the pelvis, well-circumscribed with marked flow on Doppler. Additionally, a 10.7 × 5.8 cm tubular structure containing anechoic fluid with septations was seen in the left adnexa, and a 1.2 cm Nabothian cyst was found in the cervix. No fibroids were seen.

Further workup was done with a computed tomography (CT) scan of the abdomen and pelvis with contrast (Fig. 1). The scan showed an irregular hypodense mass lesion with central hypodensity and vivid peripheral enhancement, measuring 7.8 × 7.2 × 6.2 cm, inferior to the bifurcation of the aorta at the lumbosacral junction of the prevertebral area. There was adjacent perilesional fat stranding. Furthermore, an elongated cystic tubular structure measuring approximately 4.5 × 7.5 cm was noted in the left adnexa. The left and right ovaries were not separately visualized during the scan.

The patient was advised of a Ga-DOTATATE Positron emission tomography/Computed tomography (PET/CT) scan, which revealed the primary tumor in the pelvis (Fig. 2) and several distant bony metastases.

The Ga-DOTATATE PET/CT reports showed:

- A heterogeneous density mass with marked DOTA NOC avidity and central necrosis is noted in the pelvis in the prevertebral region in the Fig. 2. It is abutting the bladder and adjacent gut loops.
- Multiple lytic lesions with marked tracer avidity are seen in the visualized skeleton, including the T6 vertebrae, Left Humeral Head, Superior Ramus of the Right Mandible, Right Ischium, Right Acetabulum and T4 vertebrae in the Figs. 3-8 respectively.

Exploratory laparotomy was performed on this patient after 2 weeks of alpha-blocker treatment to remove the primary tumor, and a brown tan mass was found in the lower abdominopelvic region below the aortic bifurcation, which was surgically excised. Biopsy of the mass was done and its

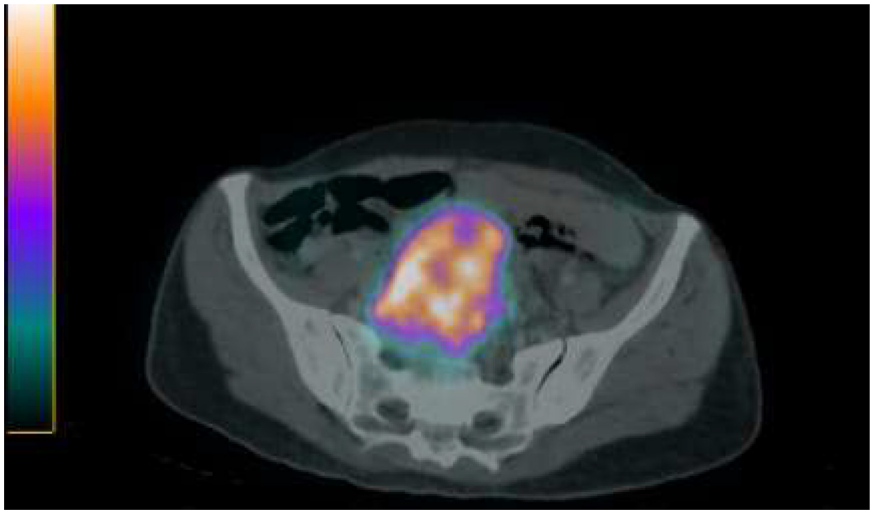

Fig. 2 – DOTA scan shows heterogeneous density mass and central necrosis which is noted in pelvis in the prevertebral region. It is abutting the bladder and adjacent gut loops.

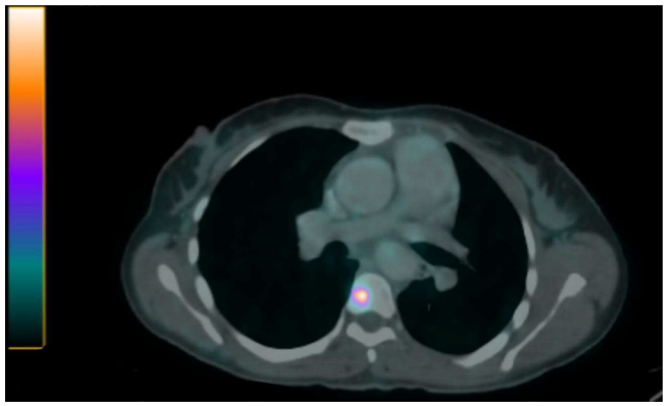

Fig. 3 – DOTA scan shows metastasis on T6.

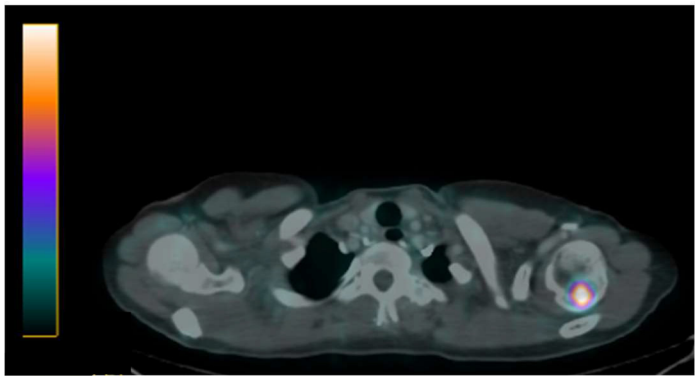

Fig. 4 – DOTA scan shows metastasis on left humeral head.

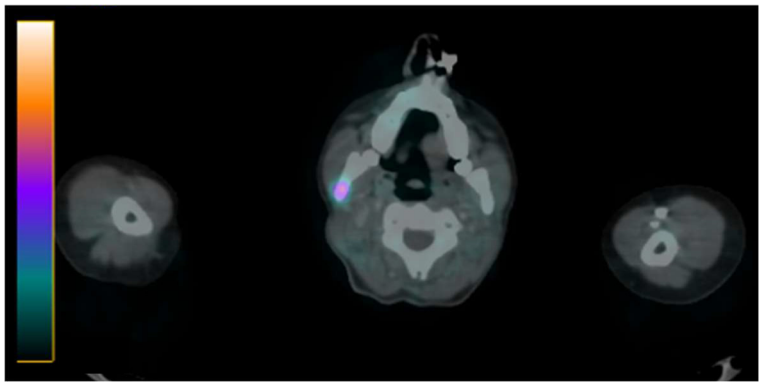

Fig. 5 – DOTA scan shows metastasis on right mandible ramus.

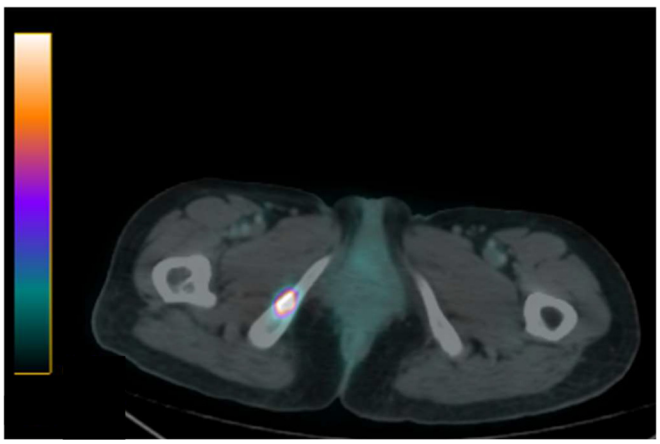

Fig. 6 – DOTA scan shows metastasis on right ischium.

histopathology is given in the Fig. 9. The surgery went uneventful, and the patient was discharged after 3 days of hospital stay and close monitoring. Follow-up of the patient showed significant improvement in her symptoms. Chemotherapy was advised to the patient to manage the bony metastasis, which was declined by the patient.

Discussion

Pheochromocytomas are rare tumors that originate from the chromaffin cells of the adrenal medulla and secrete catecholamines. The vast majority of the cases arise from the adrenal medulla, but rarely, in about 10% of the cases, they appear in an extra-adrenal location and are termed paragangliomas. Nearly half of these paragangliomas arise from the organ of Zuckerkandl, which is a mass of chromaffin cells that span from the superior mesenteric artery or renal arteries to the aortic bifurcation. Depending on their origin, paragangliomas can be sympathetic or parasympathetic. Sympathetic paragangliomas mainly secrete epinephrine, while parasympathetic ones predominantly secrete dopamine [2]. Parasympathetic paragangliomas are typically found in the head and neck region, causing palpable neck masses, tinnitus, and cranial nerve palsies. On the other hand, sympathetic paragangliomas can be found anywhere along the sympathetic chain and present with the classic pentad of headaches, palpitations, diaphoresis, pallor, and orthostasis.

When pheochromocytoma or paragangliomas are suspected, biochemical evaluation should be done, which establishes the diagnosis. Diagnosis requires a demonstra-

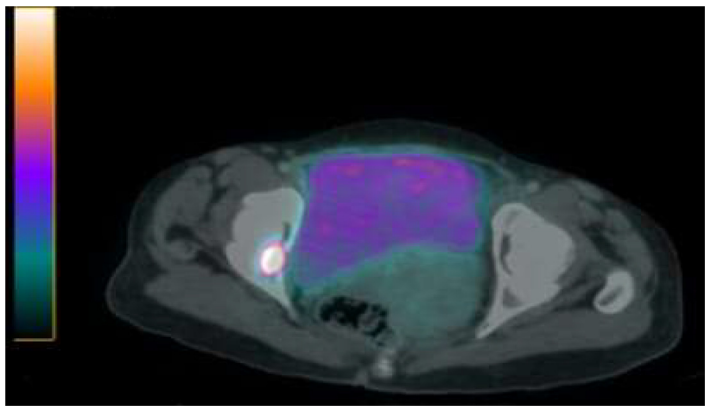

Fig. 7 – DOTA scan shows metastasis on right acetabulum.

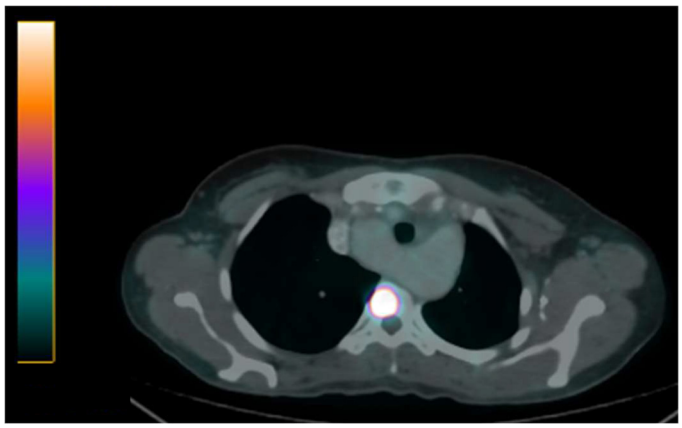

Fig. 8 – DOTA scan shows metastasis on T4.

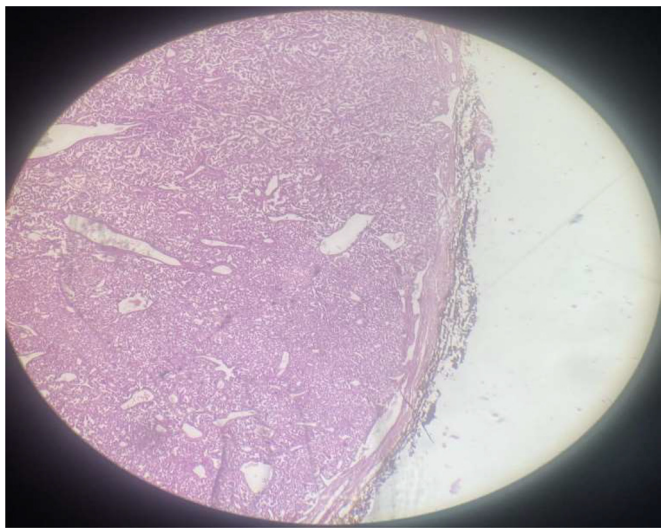

Fig. 9 – Scanner view showing (4x) showing encapsulated lesion.

tion of excess catecholamine production. Urine and plasma metanephrines, which are metabolites of catecholamines, are typically done. The reason metanephrines are evaluated is because the levels of catecholamines fluctuate, but their metabolism remains relatively constant. Normetanephrine and vanillylmandelic acid levels are also assessed. Once the diagnosis is biochemically confirmed, imaging studies should be done to locate the tumor. Conventional imaging studies with CT and MRI are done first. CT and MRI have a high sensitivity, in the range of 98%-100% for pheochromocytoma and 92%-94% for extra-adrenal paraganglioma. However, they have a limited specificity due to a significant overlap of contrast enhancement with other adrenal lesions [3]. On nonenhanced CT, the mass may range from low density to soft tissue attenuation. Two-thirds of Pheochromocytomas are solid, while the rest are complex or cystic. Contrast-enhanced CT may further reveal either a homogenous mass or variable enhancement.

On MRI, pheochromocytomas demonstrate hypointense signals on T1-weighted images and hyperintense signals on T2-weighted images. Despite its high sensitivity, the lack of characteristic appearance on MRI makes it nonspecific for diagnosing pheochromocytoma [4]. In approximately 10% of cases, pheochromocytoma manifests as a hyperintense lesion resembling a “light bulb” on T2 weighted MRI scans, resulting from increased water content due to necrosis and cystic degeneration. While this sign is not consistently present, it can help diagnose about two-thirds of pheochromocytomas. Another characteristic feature observed in both T1 and T2 weighted images is the “salt-and-pepper” appearance seen in paragangliomas. This appearance arises from the presence of small areas with low signal intensity, indicating flow voids in tumor vascularity, as well as hyperintense signal areas corresponding to tumor hemorrhage. Due to nonspecific imaging appearances, functional imaging using I-131 or I-132 radiolabeled meta-iodobenzylguanidine (MIBG) and, more recently, F-fluorodopamine and F-fluorodopa positron emission tomography (18F-DOPA PET) have been used to detect metastatic Pheochromocytomas and Paragangliomas with substantial sensitivity and specificity [4].

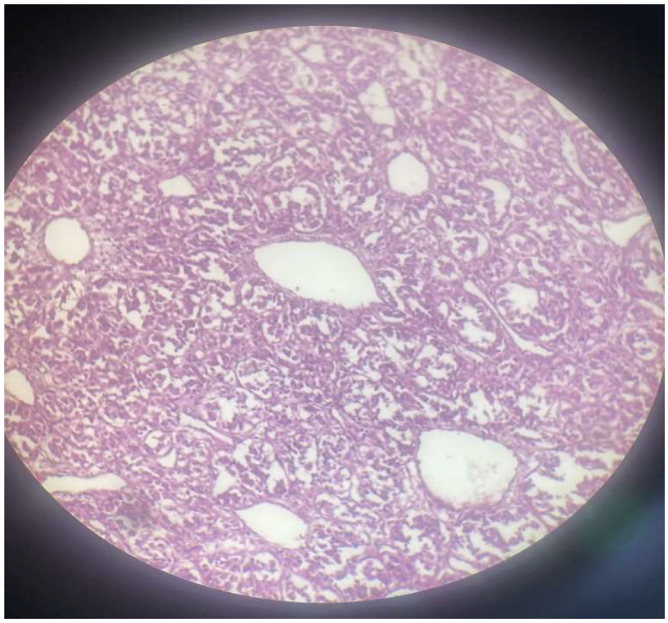

Fig. 10 – Low Power (10x) view showing nested (zellballen pattern). Nests outlined with sustentacular cells. Cells are large, polygonal, uniform and extensively vacuolated. Cytoplasm is abundant, fine and granular. Nuclei are uniform, few exhibit extensive variation in size, round to oval nuclei, nucleoli prominent.

Moreover, Ga-DOTATATE PET/CT is rapidly emerging as the preferred functional imaging technique for the identification and characterization of various neuroendocrine tumors, including Pheochromocytomas and Paragangliomas. This preference stems from its enhanced spatial resolution, improved ability to detect lesions, and advanced quantification capabilities. Ga-DOTATATE PET/CT also offers advantages in terms of convenience and patient safety. Unlike other imaging methods like octreoscan or MIBG studies that may take up to 2 days, Ga-DOTATATE PET can be completed in less than 2 hours. Additionally, it exposes patients to lower levels of radiation compared to alternative imaging techniques.

Genetic testing is recommended once a pheochromocytoma is identified because a significant percentage of patients (35%-40%) have a germline mutation associated with an increased risk of transmission and malignancy [5]. Several familial disorders, including von Hippel-Lindau syndrome, multiple endocrine neoplasia type 2, and neurofibromatosis type 1, are associated with adrenal pheochromocytomas. Although most tumors are benign, about 10% of pheochromocytomas are malignant, and the only reliable clue to the presence of malignant pheochromocytoma is a local invasion into surrounding tissues and organs or distant metastases documented on nuclear imaging.

Treatment of choice is surgical resection, which is done by laparoscopy or laparotomy and has a curative success rate of 90% in most cases. Before surgery, it is essential to administer appropriate medical therapy to prevent complications arising from the release of catecholamines during the surgical procedure, as these can lead to hypertensive crises or arrhythmias [3]. Medical preoperative treatment should be initiated 2 weeks before the scheduled surgery. The primary method of choice is treatment with alpha-adrenergic blockade, such as phenoxybenzamine or doxazosin. In some cases, adding beta-adrenergic blockers may be necessary to prevent reflex tachycardia, a potential side effect of alpha-adrenergic blockade. Following surgical resection, it is recommended to reevaluate plasma metanephrine levels 2-4 weeks postoperatively. Normal levels indicate a successful removal of the tumor.

Moreover, hypotension may occur in 20%-70% of cases after surgery. The abrupt withdrawal of catecholamines following tumor removal can result in rebound hyperinsulinemia, which, combined with depleted glycogen stores, can potentially lead to severe hypoglycemia during the postoperative period. Therefore, it is essential to monitor arterial pressure and blood sugar levels as a mandatory precaution following surgery [6].

Patients who have unresectable tumors or metastatic disease without curative treatment options can undergo chemotherapy or receive palliative systemic therapies such as I^{131}-MIBG. I^{131}-MIBG therapy is considered the standard alternative treatment, particularly in cases where the tumor shows progression and uncontrolled tumor function, and it has minimal adverse effects [3]. Before administering I^{131}-MIBG, it is essential to adequately control blood pressure using antihypertensive medications, including alpha-blockers and beta-blockers. Additionally, it is advisable to have short-acting alpha or beta-blockers readily available for emergency use during or after I^{131}-MIBG administration, as there is a possibility of a hypertensive crisis during the therapy. Furthermore, prophylactic antiemetics, with ondansetron being the preferred choice, should be given during I^{131}-MIBG treatment. Even in situations where there is a single tumor lesion without suspicion of malignancy, I^{131}-MIBG treatment can be a beneficial therapeutic option if surgery is not feasible for any reason.

Conclusion

Extra-adrenal pheochromocytomas, also known as paragangliomas, are rare tumors that typically arise in specific anatomical locations. These tumors are frequently detected through imaging examinations due to their characteristic sites. However, the variable clinical presentations and imaging findings of this disease pose challenges to accurate diagnosis. CT scans and particularly staining techniques (Ga-DOTATATE PET/CT scan) play vital roles in the pathological diagnosis and prognosis of extra-adrenal pheochromocytomas. Surgical resection is curative in case of localized disease, whereas palliative therapy in the form of chemotherapy and I^{131}-MIBG is advised for metastatic disease due to poorer prognosis.

Author contributions

Zayed Mohiyuddin[1] and Abdul Rehman Ahmad Akhtar[1] conceived the concept of the paper, Zayed Mohiyuddin wrote the first draft of the manuscript, and Abdul Rehman Ahmad Akhtar wrote the second draft. Muiz Khan Tareen[1] wrote the third and finalized the manuscript. Dr Kamran Malik[2] revised the draft and made revisions, gave the final approval, and agreed to the accuracy of the work.

Availability of data and materials

None.

Ethics approval and consent to participate

None.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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